03/30/09

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UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Takeda Pharmaceutical Co., Ltd
U.S. Patent No.: 6,462,058
Issued: October 8, 2002
To: FUJISHIMA ET AL.
Title: BENZIMIDAZOLE COMPOUND CRYSTAL

From: Serial No. 09/674624
Filed: June 15, 2000
Docket: 04164.0012USTE

CERTIFICATE UNDER 37 C.F.R 1.10
Express Mail mailing label number: EM 112401865 US
Date of Deposit: March 26, 2009
I hereby certify that the papers listed below are being deposited with the United States Postal Service Express Mail Post Office to Addressee service under 37 C.F.R 1.10 in an envelope addressed to: Mail Stop Patent Extension, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: _____
Name: Stephanie Samuell

52835
PATENT TRADEMARK OFFICE

Mail Stop : Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following papers are transmitted herewith:

- ☒ Transmittal Sheet in duplicate containing Certificate of Mailing
- ☒ Application for Extension of Patent Term Under 35 USC § 156 (12 pages)
- ☒ Exhibits A-F and H (40 pages)
- ☒ Sealed envelope containing proprietary material including: Coversheet (1 page), Exhibit G (1 page)
- ☒ 2 copies of all documents
- ☒ Return Postcard
- ☒ Please charge Deposit Account No. 50-3478 in the amount of $ 1,120.00 and any additional fees or credit overpayment to Deposit Account No. 50-3478.

Please charge any additional fees or credit overpayment to Deposit Account No. 50-3478. A duplicate of this sheet is enclosed.

By: _____
Name: Douglas P. Mueller
Reg. No.: 30,300
Initials: DPM/ad

Hamre, Schumann, Mueller & Larson, P.C.
P.O. Box 2902 Minneapolis, MN 55402-0902
612.455-3800

03/31/2009 SSITHIB1 00000045 503478 09674624
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(PTO TRANSMITTAL - GENERAL)

UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Takeda Pharmaceutical Co., Ltd
U.S. Patent No.: 6,462,058
Issued: October 8, 2002
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By: _____
Name: Douglas P. Mueller
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Hamre, Schumann, Mueller & Larson, P.C.
P.O. Box 2902 Minneapolis, MN 55402-0902
612.455-3800

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

APPLICANT:	Takeda Pharmaceutical Co., Ltd.
U.S. PATENT NO.	6,462,058
ISSUED:	October 8, 2002
TO:	FUJISHIMA ET AL.
FOR:	BENZIMIDAZOLE COMPOUND CRYSTAL
FROM:	Serial No. 09/674624
FILED:	June 15, 2000
ATTORNEY DOCKET NO.	04164.0012USTE

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By: _____
Name: Stephanie Samuell

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Mail Stop: Patent Extension
Commissioner of Patents
Patent Extension
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Takeda Pharmaceutical Company Limited ("Takeda" or "Applicant"), a corporation organized and existing under the laws of Japan, having its principal place of

business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japan, represents that it is the owner and assignee of the entire interest in and to the above-identified patent. Applicant was formerly called Takeda Chemical Industries Limited, which was the original assignee of U.S. Patent No. 6,462,058, and changed its name to Takeda Pharmaceutical Company Limited as of June 29, 2004. Based on this change of the corporate name, the change of name of the assignee of the above-identified patent to Applicant was recorded on January 19, 2005. A copy of the assignment of U.S. Patent No. 6,462,058 to Takeda Chemical Industries Limited (Exhibit A) and a copy of the documents filed for the change of the corporate name to Takeda Pharmaceutical Company Limited (Exhibit B) are attached hereto.

The NDA application of the Approved Product for the regulatory review by the United States Food and Drug Administration ("FDA") was filed by TAP Pharmaceutical Products Inc., which had been a 50-50 joint venture corporation between Takeda Pharmaceutical Co., Ltd. and Abbott Laboratories and had been a licensee of Applicant for the Approved Product. TAP Pharmaceutical Products Inc. was merged with Takeda Pharmaceuticals North America, Inc. and Takeda Global Research & Development Center, Inc. as of July 1, 2008 and accordingly, Takeda Pharmaceuticals North America, Inc., which is a subsidiary of Applicant, is the owner of the NDA approval of the Approval Product. A copy of the NDA approval is attached hereto as Exhibit C.

Applicant hereby petitions for extension of U.S. Patent No. 6,462,058 under 35 U.S.C. §156(d) and 37 C.F.R. §1.740 and states in part thereof as follows:

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS

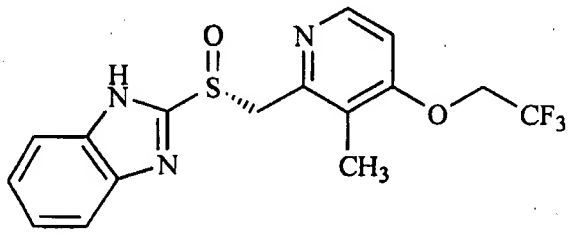
The chemical and generic name, physical structure, or characteristics of a new drug Kapidex (hereinafter sometimes referred to as "Approved Product"), which is approved by the FDA, are as follows:

The generic name of the active ingredient contained in the Approved Product is dexlansoprazole.

The chemical name of dexlansoprazole is:

2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole.

The chemical structure of dexlansoprazole is:



with a molecular formula of $C_{16}H_{14}F_3N_3O_2S$ and a molecular weight of 369.36 (based on the 2001 International Union of Pure and Applied Chemistry [IUPAC] Atomic Weight of the Elements). The approved drug Kapidex includes a crystal form of dexlansoprazole. The data of Kapidex in the NDA submitted to the FDA were produced by using the same crystalline form of dexlansoprazole as that of claim 1 in U.S. Patent No. 6,462,058.

(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED

An application for commercial marketing approval of Kapidex in the U.S. was filed pursuant to §505 (b) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. §355(b)) and reviewed under this section of the law.

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED

The commercial marketing of the Approved Product was approved on January 30, 2009 by the FDA. A copy of the FDA approval is attached hereto as Exhibit C.

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT, OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER

ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED

The Approved Product Kapidex is a sustained release formulation in a capsule using a crystalline form of dexlansoprazole as an active ingredient. This active ingredient has not been approved previously for the commercial marketing or use under the FDCA, the Public Health service Act, or the Virus-Serum-Toxin Act. Lansoprazole, a racemate of the active ingredient of the Approved Product, has been approved previously.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO § 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED

The sixty (60)-day period began on the approval date of the Approved Product January 30, 2009 and will expire on March 30, 2009. Accordingly, this application is being submitted within the 60-day period pursuant to 37 C.F.R. §1.720(f).

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION

The information of patent for which this application is submitted is as follows:

U.S. Patent No.:	6,462,058
Inventors:	Akira Fujishima
	Isao Aoki
	Keiji Kamiyama
Title:	BENZIMIDAZOLE COMPOUND CRYSTAL
Date of issue:	October 8, 2002
Date of expiration:	June 15, 2020 absent the extension

U.S. Patent No. 6,462,058 was granted on the 8th day of October2002 to Akira Fujishima, Isao Aoki, and Kenji Kamiyama and was assigned to Takeda Chemical Industries Ltd. Takeda Chemical Industries Ltd. changed the corporate name to Takeda

Pharmaceutical Co., Ltd. as of June 29, 2004, and the name change to Takeda Pharmaceutical Co. Ltd. was recorded in the United Patent Trademark Office on January 19, 2005, at Reel 015612, Frame 0101. A copy of the assignment to Takeda Chemical Industries Ltd. and the change of the corporate name are attached hereto as Exhibits A and B, respectively.

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS

A copy of the U.S. Patent No. 6,462,058, for which the extension is being sought, including the entire specification (including claims) is attached hereto as Exhibit D.

(8) A COPY OF DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT

U.S. Patent No. 6,462,058, for which this application of the patent term extension is filed, is not subject to terminal disclaimers over other U.S. Patent or U.S. Patent applications.

No certificate of correction or reexamination certificate has been issued.

A copy of documents showing payment of the maintenance fee payment for U.S. Patent No. 6,462,058 is attached hereto as Exhibit E.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS

U.S. Patent No. 6,462,058 claims, dexlansoprazole, which is an active ingredient for the Approved Product, having a particular crystalline form in claim 1, a pharmaceutical composition including the particular crystalline form of dexlansoprazole in claim 1, i.e., the Approved Product, in claim 3, a method of manufacturing the

Approved Product including dexlansoprazole having the particular crystalline form for an intended use in claim 5, and a method of using the Approved Product including dexlansoprazole having the particular crystalline form for the intended use in claim 6, as shown in Exhibit F. The claimed particular crystalline form in claim 1 is the same crystalline form as that used for the NDA of the Approved Product (see Exhibit G). Please note that the X-ray powder diffraction of dexlansoprazole in the Approved Product was measured by different equipment under different measuring conditions from those used to obtain data for U.S. Patent No. 6,462,058 and might include minor experimental deviations.

(10) A STATEMENT OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. 156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD

The information required by 37 C.F.R. §1.740(a)(10) for a patent claiming the Approved Product, a human drug Kapidex, is as follows:

(A) Effective date of the investigational new drug (IND) application and the IND number:

Effective date of IND Application: July 2, 2004

IND number: 69,927

(B) Effective date on which a new drug application (NDA) was initially filed and the NDA number:

Application date of NDA: December 28, 2007

NDA number: 22-287

(C) Date on which the NDA No. 22-287 was approved is January 30, 2009.

(11) **A BRIEF DESCRIPTION OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES**

A brief description of the significant activities undertaken by the applicant of the commercial marketing approval Takeda during the applicable regulatory period for the Approved Product and the significant dates applicable to such activities are shown in Exhibit H attached hereto.

(12) A STATEMENT THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED

Applicant is of the opinion that U.S. Patent No. 6,462,058 is eligible for the patent term extension under 35 U.S.C. §156 because the requirements of 35 U.S.C. §156 (a) and (c)(4) have been satisfied as follows:

(a) 35 U.S.C. §156(a)

U.S. Patent No. 6,462,058 claims dexlansoprazole, which is an active ingredient of a human drug Kapidex, having a particular crystalline form as defined in 37 C.F.R. §1.710, in claim 1 and a pharmaceutical composition including the particular crystalline form of dexlansoprazole, i.e., the Approved Product, in claim 3.

(b) 35 U.S.C. §156(a)(1)

U.S. Patent No. 6,462,058 has not yet expired as of the date of submission of this application.

(c) 35 U.S.C. §156(a)(2)

The term of U.S. Patent No. 6,462,058 has never been extended under 35 U.S.C. §156(e)(1).

(d) 35 U.S.C. §156(a)(3)

This application for extension of U.S. Patent No. 6,462,058 is being submitted by the owner of record Takeda Pharmaceutical Co., Ltd. through their attorneys in accordance with the requirements of 35 U.S.C. §156(d)(1) through (4).

(e) 35 U.S.C. §156(a)(4)

The Approved Product Kapidex has been subject to a regulatory review period under §505 of the FDCA (21 U.S.C. §355) before its commercial marketing or use.

(f) 35 U.S.C. §156(a)(5)(A)

The permission for the commercial marketing or use of the Approved Product after such regulatory review period is the first permitted commercial

marketing or use of the Approved Product and the active ingredient of the Approved Product dexlansoprazole under §505 of the FDCA (21 U.S.C. §355).

(g) 35 U.S.C. §156(c)(4)

To the date of this application, there is no other U.S. patent that has been extended under 35 U.S.C. §156(e)(1) for the same regulatory review period for the Approved Product. Applicant acknowledges that applications for extension of U.S. Patent Nos. 6,664,276 and 6,939,971 are being filed based on the same regulatory review period, and confirms that Applicant will elect one of the three for grant.

Applicant further is of the opinion that U.S. Patent No. 6,462,058 is entitled to the patent term extension under 35 U.S.C. §156 for the length of 959 days extended from June 15, 2020 as determined pursuant to 37 C.F.R. §1.775 by the following:

(a) 37 C.F.R. §1.775(b)

The number of days in the period beginning on the effective date of the IND application for the Approved Product July 2, 2004 and ending on December 28, 2007, which is the date of the initial NDA application for the Approved Product was filed under §505(b) of the FDCA, is 1275 days ("Period (c)-1" as defined under 35 U.S.C. §156(g)(1)(B)(i)).

The number of days in the period beginning on the date of the NDA application for the Approved Product December 28, 2007 and ending on the approval date of the NDA January 30, 2009 is 400 days ("Period (c)-2" as defined under 35 U.S.C. §156(g)(1)(B)(ii)).

(b) 37 C.F.R. §1.775(d)(1)

The term of extension of U.S. Patent No. 6,462,058 is determined by subtracting the number of days of (i)-(iii) below from the total period of Period (c)-1 and Period (c)-2.

(i) The number of days in Periods (c)-1 and (c)-2 on and before the issue date of U.S. Patent No. 6,462,058 October 8, 2002 is zero (0) day.

(ii) The number of days in Period (c)-1 and (c)-2 during which Applicant did not act with due diligence is zero (0) day.

(iii) One-half (1/2) the number of days remaining in the Period (c)-1 after reduced by the days of (b)-(i) and (ii) above is 637 days.

Accordingly, the extension period is 1038 days, calculated by subtracting 637 days from 1675 days (Periods (c)-1 and (c)-2: 1275 + 400 days).

(c) 37 C.F.R. §1.775(d)(2)

U.S. Patent No. 6,462,058 filed on June 15, 2000 is not subject to a terminal disclaimer. The extended expiration date of U.S. Patent No. 6,462,058 obtained by adding 1038 days to June 15, 2020 is April 19, 2023.

(d) 37 C.F.R. §1.775(d)(3)

The extended date calculated by adding 14 years to the NDA approval date January 30, 2009 is January 30, 2023.

(e) 37 C.F.R. §1.775(d)(4)

The earlier date of the extended expiration dates of U.S. Patent No. 6,462,058 in (c) and (d) above is January 30, 2023.

(f) 37 C.F.R. §1.775(d)(5)

The earlier date of the extended expiration dates of U.S. Patent No. 6,462,058 in (e) and the date June 15, 2025 calculated by adding five (5) years to the current expiration date June 15, 2020 is January 30, 2023.

In light of the (a)-(e) above, Applicant is in the opinion that the extended expiration date of U.S. Patent No. 6,462,058 should January 30, 2023, i.e., 959 days or 2 years and 229 days from the date of the current expiration date June 15, 2020.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension of U.S. Patent No. 6,462,058 being sought.

(14) **THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION**

Please charge Deposit Account No. 50-3478 in the amount of $ 1,120.00 and any additional fees or credit overpayment to Deposit Account No. 50-3478.

(15) **THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED**

Please address all inquires and correspondence relating to this application for patent term extension to:

Douglas P. Mueller
HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902
Minneapolis, MN 55402-0902
(612) 455-3800

(16) **THE APPLICATION UNDER THIS SECTION MUST BE ACCOMPANIED BY TWO ADDITIONAL COPIES OF SUCH APPLICATION**

Two additional copies of this application are attached hereto.

Respectfully submitted,

HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902
Minneapolis, MN 55402-0902
(612) 455-3800

Dated: March 26, 2009

By: _____
Douglas P. Mueller
Reg. No. 30,300

DPM/my

EXHIBIT A

ASSIGNMENT

For good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each undersigned inventor hereby sells and assigns, to TAKEDA CHEMICAL INDUSTRIES LTD., a corporation of Japan, 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan (hereinafter ASSIGNEE) all right, title and interest for the United States, its territories and possessions in and to the following invention and U.S. application filed thereon, and the entire right, title and interest in and to any and all Letters Patents which may be granted therefor in the United States, to be held and enjoyed by said ASSIGNEE, its successors, legal representatives and assigns to the full end of the term or terms for which any and all such Letters Patent may be granted as fully and entirely as would have been held and enjoyed by the undersigned had this Assignment not been made.

Title of Invention : Benzimidazole Compound Crystal

United States Patent Application :

[XX] executed concurrently herewith
[ ] executed on _____
[ ] Serial No. _____ Filed _____

Each of the undersigned acknowledges that this sale and assignment includes any and all divisions or continuations of said United States Patent application, and any and all Letters Patent of the United States which may issue on any such applications, including any and all reissues or extensions thereof.

Each of the undersigned hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all such Letters Patent to said ASSIGNEE, its successors or assigns in accordance herewith;

Each of the undersigned warrants and covenants that he has the full and unencumbered right to sell and assign the interests herein sold and assigned and that he has not executed and will not execute any document or instrument in conflict herewith;

Each of the undersigned further covenants and agrees he will communicate to said ASSIGNEE, its successors, legal representatives or assigns all information known to him relating to said invention or patent application and that he will execute and deliver any papers, make all rightful oaths, assist in and testify in any related proceedings including interferences or lawsuits concerning this application or continuation, division or reissue thereof, and perform all other lawful acts deemed necessary or desirable by said ASSIGNEE, its successors, legal representatives or assigns to obtain a grant of a valid United States Patent on said invention;

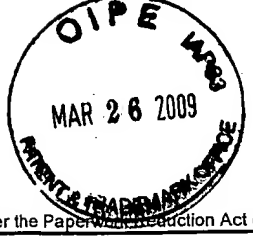
Each of the undersigned hereby grants ASSIGNEE and its legal representatives, the power to insert in this Assignment any further identification which may be necessary or desirable to comply with the rules of the U.S. Patent and Trademark Office for recordation of this Assignment and specifically, the power to insert in the space provided above, the filing date and application number of the application when known.

In witness hereof, executed by the undersigned on the date(s) opposite the undersigned names.

NAMES AND SIGNATURES OF INVENTORS		
1.Name: Akira FUJISHIMA	Signature: Akira Fujishima	Date: November 1, 2000
2.Name: Isao AOKI	Signature: Isao Aoki	Date: November 1, 2000
3.Name: Keiji KAMIYAMA	Signature: Keiji Kamiyama	Date: November 1, 2000
4.Name:	Signature:	Date:
5.Name:	Signature:	Date:
6.Name:	Signature:	Date:
NAMES AND SIGNATURES OF WITNESSES*		
Name/ Yuji NISHIKIMI For: 1 - 3	Signature: Yuji Nishikimi	Date: November 1, 2000
Name/ Yasunori GOTO For: 1 - 3	Signature: Yasunori Goto	Date: November 1, 2000
Name/ For:	Signature:	Date:
Name/ For:	Signature:	Date:
Name/ For:	Signature:	Date:
Name/ For:	Signature:	Date:

*Notice for Witnesses! Please indicate which inventor(s) you are signing for by writing the corresponding numbers after "For:"

EXHIBIT B



PTO/SB/96 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: TAKEDA PHARMACEUTICAL COMPANY LIMITED

Application No./Patent No.: 6,462,058 Filed/Issue Date: OCTOBER 08, 2002

Entitled: BENZIMIDAZOLE COMPOUND CRYSTAL

TAKEDA PHARMACEUTICAL COMPANY LIMITED, a CORPORATION
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:
1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest
(The extent (by percentage) of its ownership interest is_____ %)

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: INVENTORS To: TAKEDA CHEMICAL INDUSTRIES LTD.
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: TAKEDA CHEMICAL INDUSTRIES LTD. To: TAKEDA PHARMACEUTICAL COMPANY LIMITED
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

_____	DECEMBER 7, 2006
Signature	Date
DOUGLAS P. MUELLER	612.455.3804
Printed or Typed Name	Telephone Number
ATTORNEY FOR APPLICANT	
Title	

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPAN.
FAX : (06)6944-6248 TEL : (06)6944-6411
URL : http://www.osaka.cci.or.jp/

October 13, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP

This is to certify that the undermentioned company is registered as a member of this Chamber.

Company name: Takeda Pharmaceutical Company Limited

(The former company name in English was Takeda Chemical Industries, Ltd. until June 29, 2004.)

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Membership Number: KT-01-00080

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

AD 0078 76

EXHIBIT C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-287

NDA APPROVAL

Takeda Global Research and Development Center, Inc
Attention: Nancianne Knipfer, Ph.D., RAC
Manager, Regulatory Affairs Strategy
One Takeda Parkway
Deerfield, IL 60015

Dear Dr. Knipfer:

Please refer to your new drug application (NDA) dated December 28, 2007, received December 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kapidex (dexlansoprazole) Delayed Release Capsules 30, 60, and 90 mg.

We acknowledge receipt of your submissions dated February 5, 18, 19, 2008; March 7 and 26, 2008; April 28 and 29, 2008; May 22 and 30, 2008; June 24, 26, 30, 2008; July 11 and 15, 2008; August 21 and 26, 2008; September 9, 10, 26, 2008; October 20 and 21, 2008; November 7, 14, 21, 2008; December 10, 17, 23, 2008 and January 12, 13, 14, 22, 23, 27, 28, 2009.

This new drug application provides for the use of Kapidex (dexlansoprazole) Delayed Release Capsules 30 mg for maintaining healing of erosive esophagitis, and for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD). This new drug application also provides for the use of Kapidex (dexlansoprazole) Delayed Release Capsules 60 mg for healing of all grades of erosive esophagitis.

As discussed in the November 5, 2008 teleconference, we are not approving the 90 mg dose of Kapidex (dexlansoprazole) Delayed Release Capsules.

We have completed our review of this application, as amended. It is approved for the 30 and 60 mg doses, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than one month for the following indications: healing and maintenance of healing of all grades of erosive esophagitis (EE) and treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) because the necessary studies are impossible or highly impractical.

We are waiving the pediatric study requirement for ages 1-11 months for the following indications: healing and maintenance of healing of all grades of erosive esophagitis (EE) because necessary studies are impossible or highly impractical. The number of pediatric patients with erosive esophagitis in this age group would be limited.

We are deferring submission of your pediatric studies for ages 1 year to 17 years for healing and maintenance of healing of all grades of erosive esophagitis (EE) and for 1 month to 17 years for treating heartburn associated with non-erosive gastroesophageal disease (GERD) because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 1 year to 11 years.

   Final report submission: October 31, 2013

2. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 12 years to 17 years.

   Final report submission: March 31, 2013

3. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 month to 11 months.

   Final report submission: July 31, 2016

4. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 year to 11 years.

   Final report submission: October 31, 2013

5. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.

   Final report submission: March 31, 2013

Submit final study reports to your NDA 22-287. Use the following designator to prominently label all submissions:

Required Pediatric Assessments

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk for bone fractures in patients who have prolonged use and/or higher doses of Kapidex (dexlansoprazole) Delayed Release Capsules.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing clinical trial:

6. A clinical trial to evaluate the effect of Kapidex (dexlansoprazole) Delayed Release Capsules on bone homeostasis. The primary endpoint will be biomarkers of bone formation and bone resorption. Treatments will include: placebo, dexlansoprazole and esomeprazole.

The timetable you submitted on January 12, 2009, states that you will conduct this trial according to the following timetable:

Final protocol Submission:	August 31, 2009
Trial Start Date:	October 31, 2009
Final Report Submission:	December 31, 2011

Submit the protocol to your IND 69,927, with a cross-reference letter to this NDA 22-287. Submit all final reports to your NDA 22-287. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-287."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the January 13, 2009 submitted carton and immediate container labels, with the exception of the Hospital Unit Dose Blister Labels for 30 mg and 60 mg doses, of which we accept the January 23, 2009 submission as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 22-287".** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Anna Simon, Regulatory Project Manager, at (301) 796-3509.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KAPIDEX safely and effectively. See full prescribing information for KAPIDEX.

KAPIDEX (dexlansoprazole) delayed release capsules
Initial U.S. Approval: 1995 (lansoprazole)

INDICATIONS AND USAGE

KAPIDEX is a proton pump inhibitor (PPI) indicated for:

- Healing of all grades of erosive esophagitis (EE). (1.1)
- Maintaining healing of EE. (1.2)
- Treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD). (1.3)

DOSAGE AND ADMINISTRATION

- Healing of EE: 60 mg once daily for up to 8 weeks. (2.1)
- Maintenance of healed EE: 30 mg once daily for up to 6 months. (2.1)
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks. (2.1)
- Hepatic impairment: Consider 30 mg maximum daily dose for patients with moderate hepatic impairment (Child-Pugh Class B). No studies were conducted in patients with severe hepatic impairment (Child-Pugh Class C). (2.2, 8.7)
- KAPIDEX can be taken without regard to food. (2.3)
- KAPIDEX should be swallowed whole. Alternatively, capsules can be opened, sprinkled on one tablespoon of applesauce, and swallowed immediately. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 30 mg and 60 mg. (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to any component of the formulation. (4)

WARNINGS AND PRECAUTIONS

Gastric malignancy: Symptomatic response with KAPIDEX does not preclude the presence of gastric malignancy. (5.1)

ADVERSE REACTIONS

Most commonly reported adverse reactions (≥2%): diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1.877.825.3328 or FDA at 1.800.FDA.1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Atazanavir: Do not co-administer with KAPIDEX because atazanavir systemic concentrations may be substantially decreased. (7.1)
- Drugs with pH-dependent absorption (e.g., ampicillin esters, digoxin, iron salts, ketoconazole): KAPIDEX may interfere with absorption of drugs for which gastric pH is important for bioavailability. (7.1)
- Warfarin: Patients taking concomitant warfarin may require monitoring for increases in international normalized ratio (INR) and prothrombin time. (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.4)
- Pediatric use: Safety and effectiveness not established in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 1/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Healing of Erosive Esophagitis

KAPIDEX is indicated for healing of all grades of erosive esophagitis (EE) for up to 8 weeks.

1.2 Maintenance of Healed Erosive Esophagitis

KAPIDEX is indicated to maintain healing of EE for up to 6 months.

1.3 Symptomatic Non-Erosive Gastroesophageal Reflux Disease

KAPIDEX is indicated for the treatment of heartburn associated with non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

KAPIDEX is available as capsules in 30 mg and 60 mg strengths for adult use. Directions for use in each indication are summarized in Table 1.

Table 1: KAPIDEX Dosing Recommendations

Indication	Recommended Dose	Frequency
Healing of EE	60 mg	Once daily for up to 8 weeks
Maintenance of Healed EE	30 mg	Once daily*
Symptomatic Non-Erosive GERD	30 mg	Once daily for 4 weeks

*Controlled studies did not extend beyond 6 months.

2.2 Special Populations

No adjustment for KAPIDEX is necessary for patients with mild hepatic impairment (Child-Pugh Class A). Consider a maximum daily dose of 30 mg for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)]*.

No dosage adjustment is necessary for elderly patients or for patients with renal impairment *[see Clinical Pharmacology (12.5)]*.

2.3 Important Administration Information

KAPIDEX can be taken without regard to food.
KAPIDEX should be swallowed whole.

- Alternatively, KAPIDEX capsules can be opened and administered as follows:
  - Open capsule;
  - Sprinkle intact granules on one tablespoon of applesauce;
  - Swallow immediately.

3 DOSAGE FORMS AND STRENGTHS

- 30 mg capsules are opaque, blue and gray with TAP and "30" imprinted on the capsule.
- 60 mg capsules are opaque, blue with TAP and "60" imprinted on the capsule.

4 CONTRAINDICATIONS

KAPIDEX is contraindicated in patients with known hypersensitivity to any component of the formulation *[see Description (11)]*. Hypersensitivity and anaphylaxis have been reported with KAPIDEX use *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Gastric Malignancy

Symptomatic response with KAPIDEX does not preclude the presence of gastric malignancy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of KAPIDEX was evaluated in 4548 patients in controlled and uncontrolled clinical studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on KAPIDEX 30 mg, 2218 patients on KAPIDEX 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly

compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Most Commonly Reported Adverse Reactions

The most common adverse reactions (≥2%) that occurred at a higher incidence for KAPIDEX than placebo in the controlled studies are presented in Table 2.

Table 2: Incidence of Treatment-Emergent Adverse Reactions in Controlled Studies

Adverse Reaction	Placebo (N=896) %	KAPIDEX 30 mg (N=455) %	KAPIDEX 60 mg (N=2218) %	KAPIDEX Total (N=2821) %	Lansoprazole 30 mg (N=1383) %
Diarrhea	2.9	5.1	4.7	4.8	3.2
Abdominal Pain	3.5	3.5	4.0	4.0	2.6
Nausea	2.6	3.3	2.8	2.9	1.8
Upper Respiratory Tract Infection	0.8	2.9	1.7	1.9	0.8
Vomiting	0.8	2.2	1.4	1.6	1.1
Flatulence	0.6	2.6	1.4	1.6	1.2

Adverse Reactions Resulting in Discontinuation

In controlled clinical studies, the most common adverse reaction leading to discontinuation from KAPIDEX therapy was diarrhea (0.7%).

Other Adverse Reactions

Other adverse reactions that were reported in controlled studies at an incidence of less than 2% are listed below by body system:

Blood and Lymphatic System Disorders: anemia, lymphadenopathy
Cardiac Disorders: angina, arrhythmia, bradycardia, chest pain, edema, myocardial infarction, palpitation, tachycardia
Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo
Endocrine Disorders: goiter
Eye Disorders: eye irritation, eye swelling
Gastrointestinal Disorders: abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, bowel sounds abnormal, breath odor, colitis microscopic, colonic polyp, constipation, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation, esophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GERD, GI ulcers and perforation, hematemesis, hematochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, nausea and vomiting, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage
General Disorders and Administration Site Conditions: adverse drug reaction, asthenia, chest pain, chills, feeling abnormal, inflammation, mucosal inflammation, nodule, pain, pyrexia
Hepatobiliary Disorders: biliary colic, cholelithiasis, hepatomegaly
Immune System Disorders: hypersensitivity
Infections and Infestations: candida infections, influenza, nasopharyngitis, oral herpes, pharyngitis, sinusitis, viral infection, vulvo-vaginal infection
Injury, Poisoning and Procedural Complications: falls, fractures, joint sprains, overdose, procedural pain, sunburn
Laboratory Investigations: ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase
Metabolism and Nutrition Disorders: appetite changes, hypercalcemia, hypokalemia
Musculoskeletal and Connective Tissue Disorders: arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia
Nervous System Disorders: altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia
Psychiatric Disorders: abnormal dreams, anxiety, depression, insomnia, libido changes
Renal and Urinary Disorders: dysuria, micturition urgency
Reproductive System and Breast Disorders: dysmenorrhea, dyspareunia, menorrhagia, menstrual disorder
Respiratory, Thoracic and Mediastinal Disorders: aspiration, asthma, bronchitis, cough, dyspnoea, hiccups, hyperventilation, respiratory tract congestion, sore throat
Skin and Subcutaneous Tissue Disorders: acne, dermatitis, erythema, pruritis, rash, skin lesion, urticaria
Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study and were considered related to KAPIDEX by the treating physician included: anaphylaxis, auditory hallucination, B-cell lymphoma, central obesity, cholecystitis acute, decreased hemoglobin, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gastrointestinal pain, gout, herpes zoster, hyperglycemia, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, oral soft tissue disorder, rectal tenesmus, restless legs syndrome, somnolence, thrombocythemia, tonsillitis.

Other adverse reactions not observed with KAPIDEX, but occurring with the racemate lansoprazole can be found in the lansoprazole package insert, ADVERSE REACTIONS section.

7 DRUG INTERACTIONS

7.1 Drugs with pH-Dependent Absorption Pharmacokinetics

KAPIDEX causes inhibition of gastric acid secretion. KAPIDEX is likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, KAPIDEX should not be co-administered with atazanavir.

It is theoretically possible that KAPIDEX may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole).

7.2 Warfarin

Co-administration of KAPIDEX 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR *[see Clinical Pharmacology (12.6)]*. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with KAPIDEX and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B. There are, no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, KAPIDEX should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to 30 mg per kg per day (approximately 9-fold the maximum recommended human dexlansoprazole dose [60 mg] based on body surface area [BSA]) revealed no evidence of harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 150 mg per kg per day (40 times the recommended human dose based on BSA) and in pregnant rabbits at oral lansoprazole doses up to 30 mg per kg per day (16 times the recommended human dose based on BSA) revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

8.3 Nursing Mothers

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies *[see Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)]*, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of KAPIDEX in pediatric patients (less than 18 years of age) have not been established.

8.5 Geriatric Use

In clinical studies of KAPIDEX, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.5)]*.

8.6 Renal Impairment

No dosage adjustment of KAPIDEX is necessary in patients with renal impairment. The pharmacokinetics of dexlansoprazole in patients with renal impairment are not expected to be altered since dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole *[see Clinical Pharmacology (12.5)]*.

8.7 Hepatic Impairment

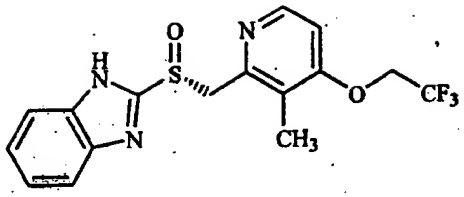
No dosage adjustment for KAPIDEX is necessary for patients with mild hepatic impairment (Child-Pugh Class A). KAPIDEX 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) *[see Clinical Pharmacology (12.5)]*.

10 OVERDOSAGE

There have been no reports of significant overdose of KAPIDEX. Multiple doses of KAPIDEX 120 mg and a single dose of KAPIDEX 300 mg did not result in death or other severe adverse events . Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

11 DESCRIPTION

The active ingredient in KAPIDEX (dexlansoprazole) delayed release capsules is (+)-2-[(*R*)-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl] sulfinyl]-*1H*-benzimidazole, a compound that inhibits gastric acid secretion. Dexlansoprazole is the *R*-enantiomer of lansoprazole (a racemic mixture of the *R*- and *S*-enantiomers). Its empirical formula is: $C_{16}H_{14}F_3N_3O_2S$, with a molecular weight of 369.36. The structural formula is:



Dexlansoprazole is a white to nearly white crystalline powder which melts with decomposition at 140°C. Dexlansoprazole is freely soluble in dimethylformamide, methanol, dichloromethane, ethanol, and ethyl acetate; and soluble in acetonitrile; slightly soluble in ether; and very slightly soluble in water; and practically insoluble in hexane.

Dexlansoprazole is stable when exposed to light. Dexlansoprazole is more stable in neutral and alkaline conditions than acidic conditions.

KAPIDEX is supplied as a dual delayed release formulation in capsules for oral administration. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles *[see Clinical Pharmacology (12.3)]*.

KAPIDEX is available in two dosage strengths: 30 mg and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient) and the following inactive ingredients: sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymer, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The components of the capsule shell include the following inactive ingredients: hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No. 2 and aluminum lake; gray contains ferric oxide and aluminum lake; and both contain titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexlansoprazole is a PPI that suppresses gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, dexlansoprazole blocks the final step of acid production.

12.2 Pharmacodynamics

Antisecretory Activity
The effects of KAPIDEX 60 mg (n = 20) or lansoprazole 30 mg (n = 23) once daily for five days on 24-hour intragastric pH were assessed in healthy subjects in a multiple-dose crossover study. The results are summarized in Table 3.

Table 3: Effect on 24-hour Intragastric pH on Day 5 After Administration of KAPIDEX or Lansoprazole

KAPIDEX 60 mg	Lansoprazole 30 mg
Mean Intragastric pH	
4.55	4.13
% Time Intragastric pH > 4 (hours)	
71 (17 hours)	60 (14 hours)

Serum Gastrin Effects
The effect of KAPIDEX on serum gastrin concentrations was evaluated in approximately 3480 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with KAPIDEX 30 mg and 60 mg doses. In patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Enterochromaffin-Like Cell (ECL) Effects
There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with KAPIDEX 30 mg, 60 mg or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats *[see Nonclinical Toxicology (13.1)]*.

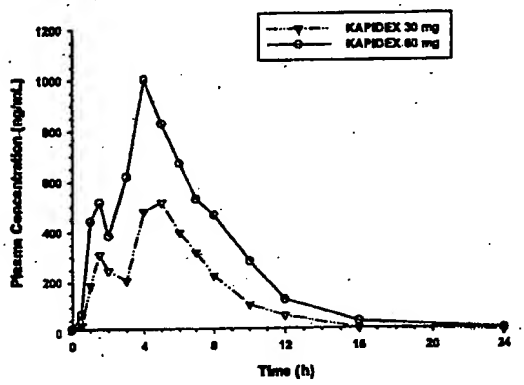
Effect on Cardiac Repolarization
A study was conducted to assess the potential of KAPIDEX to prolong the QT/QT_c interval in healthy adult subjects. KAPIDEX doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QT_c intervals compared to placebo.

12.3 Pharmacokinetics

The dual delayed release formulation of KAPIDEX results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours (see Figure 1). Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once

daily doses of KAPIDEX 30 mg or 60 mg, although mean AUC_t and C_{max} values of dexlansoprazole were slightly higher (less than 10%) on day 5 than on day 1.

Figure 1: Mean Plasma Dexlansoprazole Concentration – Time Profile Following Oral Administration of 30 or 60 mg KAPIDEX Once Daily for 5 Days in Healthy Subjects



The pharmacokinetics of dexlansoprazole are highly variable, with percent coefficient of variation (CV%) values for C_{max}, AUC, and CL/F of greater than 30% (see Table 4).

Table 4: Mean (CV%) Pharmacokinetic Parameters for Subjects on Day 5 After Administration of KAPIDEX

Dose (mg)	C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	CL/F (L/h)
30	658 (40%) (N=44)	3275 (47%) (N=43)	11.4 (48%) (N=43)
60	1397 (51%) (N=79)	6529 (60%) (N=73)	11.6 (46%) (N=41)

Absorption
After oral administration of KAPIDEX 30 mg or 60 mg to healthy subjects and symptomatic GERD patients, mean C_{max} and AUC values of dexlansoprazole increased approximately dose proportionally (see Figure 1).

Distribution
Plasma protein binding of dexlansoprazole ranged from 96.1% to 98.8% in healthy subjects and was independent of concentration from 0.01 to 20 mcg per mL. The apparent volume of distribution (V_z/F) after multiple doses in symptomatic GERD patients was 40.3 L.

Metabolism
Dexlansoprazole is extensively metabolized in the liver by oxidation, reduction, and subsequent formation of sulfate, glucuronide and glutathione conjugates to inactive metabolites. Oxidative metabolites are formed by the cytochrome P450 (CYP) enzyme system including hydroxylation mainly by CYP2C19, and oxidation to the sulfone by CYP3A4.

CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates; extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite.

Elimination
Following the administration of KAPIDEX, no unchanged dexlansoprazole is excreted in urine. Following the administration of [^{14}C]dexlansoprazole to 6 healthy male subjects, approximately 50.7% (standard deviation (SD): 9.0%) of the administered radioactivity was excreted in urine and 47.6% (SD: 7.3%) in the feces. Apparent clearance (CL/F) in healthy subjects was 11.4 to 11.6 L/h, respectively, after 5-days of 30 or 60 mg once daily administration.

Effect of CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole
Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of KAPIDEX 30 mg or 60 mg (N=2 to 6 subjects/group), mean dexlansoprazole C_{max} and AUC values were up to 2 times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean C_{max} was up to 4 times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.

12.4 Effect of Food on Pharmacokinetics and Pharmacodynamics

In food-effect studies in healthy subjects receiving KAPIDEX under various fed conditions compared to fasting, increases in C_{max} ranged from 12% to 55%, increases in AUC ranged from 9% to 37%, and t_{max} varied (ranging from a decrease of 0.7 hours to an increase of 3 hours). No significant differences in mean intragastric pH were observed between fasted and various fed conditions. However, the percentage of time intragastric pH exceeded 4 over the 24-hour dosing interval decreased slightly when KAPIDEX was administered after a meal (57%) relative to fasting (64%), primarily due to a decreased response in intragastric pH during the first 4 hours after dosing. Because of this, while KAPIDEX can be taken without regard to food, some patients may benefit from administering the dose prior to a meal if post-meal symptoms do not resolve under post-fed conditions.

12.5 Special Populations

Pediatric Use
The pharmacokinetics of dexlansoprazole in patients under the age of 18 years have not been studied.

Geriatric Use
The terminal elimination half-life of dexlansoprazole is significantly increased in geriatric subjects compared to younger subjects (2.23 and 1.5 hours, respectively); this difference is not clinically relevant. Dexlansoprazole exhibited higher systemic exposure (AUC) in geriatric subjects (34.5% higher) than younger subjects. No dosage adjustment is needed in geriatric patients *[see Use in Specific Populations (8.5)]*.

Renal Impairment
Dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole. Therefore, the pharmacokinetics of dexlansoprazole are not expected to be altered in patients with renal impairment, and no studies were conducted in subjects with renal impairment *[see Use in Specific Populations (8.6)]*. In addition, the pharmacokinetics of lansoprazole were studied in patients with mild, moderate or severe renal impairment; results demonstrated no need for a dose adjustment for this patient population.

Hepatic Impairment
In a study of 12 patients with moderately impaired hepatic function who received a single oral dose of KAPIDEX 60 mg, plasma exposure (AUC) of bound and unbound dexlansoprazole in the hepatic impairment group was approximately 2 times greater compared to subjects with normal hepatic function. This difference in exposure was not due to a difference in protein binding between the two liver function groups. No adjustment for KAPIDEX is necessary for patients with mild hepatic impairment (Child-Pugh Class A). KAPIDEX 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7)]*.

Gender
In a study of 12 male and 12 female healthy subjects who received a single oral dose of KAPIDEX 60 mg, females had higher systemic exposure (AUC) (42.6% higher) than males. No dosage adjustment is necessary in patients based on gender.

12.6 Drug-Drug Interactions

Warfarin
In a study of 20 healthy subjects, co-administration of KAPIDEX 90 mg once daily for 11 days with a single 25 mg oral dose of warfarin on day 6 did not result in any significant differences in the pharmacokinetics of warfarin or INR compared to administration of warfarin with placebo. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly *[see Drug Interactions (7.2)]*.

Cytochrome P 450 Interactions
Dexlansoprazole is metabolized, in part, by CYP2C19 and CYP3A4 *[see Clinical Pharmacology (12.3)]*.

In vitro studies have shown that KAPIDEX is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Furthermore, clinical drug-drug interaction studies in mainly CYP2C19 extensive and intermediate metabolizers have shown that KAPIDEX does not affect the pharmacokinetics of diazepam, phenytoin, or theophylline. The subjects' CYP1A2 genotypes in the drug-drug interaction study with theophylline were not determined.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface (mg/m^2) basis of a 50 kg person of average height (1.46 m^2 BSA) given the recommended human dose of lansoprazole (30 mg per day).

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats *[see Clinical Pharmacology (12.2)]*.

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day (4 to 40 times the recommended lansoprazole human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg lansoprazole per kg per day (13 times the recommended lansoprazole human dose based on BSA) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 mg to 600 mg per kg per day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 mg and 600 mg

lansoprazole per kg per day (40 to 80 times the recommended lansoprazole human dose based on BSA) and female mice treated with 150 mg to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended lansoprazole human dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was negative in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test and the rat bone marrow cell chromosomal aberration test. Lansoprazole was positive in *in vitro* human lymphocyte chromosomal aberration tests.

Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended lansoprazole human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Healing of Erosive Esophagitis

Two multi-center, double-blind, active-controlled, randomized, 8-week studies were conducted in patients with endoscopically confirmed EE. Severity of the disease was classified based on the Los Angeles Classification Grading System (Grades A-D). Patients were randomized to one of the following three treatment groups: KAPIDEX 60 mg daily, KAPIDEX 90 mg daily or lansoprazole 30 mg daily. Patients who were *H pylori* positive or who had Barrett's Esophagus and/or definite dysplastic changes at baseline were excluded from these studies. A total of 4092 patients were enrolled and ranged in age from 18 to 90 years (median age 48 years) with 54% male. Race was distributed as follows: 87% Caucasian, 5% Black and 8% other. Based on the Los Angeles Classification, 71% of patients had mild EE (Grades A and B) and 29% of patients had moderate to severe EE (Grades C and D) before treatment.

The studies were designed to test non-inferiority. If non-inferiority was demonstrated then superiority would be tested. Although non-inferiority was demonstrated in both studies, the finding of superiority in one study was not replicated in the other.

The proportion of patients with healed EE at week 4 or 8 is presented below in Table 5.

Table 5: EE Healing Rates[a]: All Grades

Study	Number of Patients (N)[b]	Treatment Group (daily)	Week 4 % Healed	Week 8[c] % Healed	(95% CI) for the Treatment Difference (KAPIDEX – Lansoprazole) by Week 8
1	667	KAPIDEX 60 mg	70	87	(-1.5, 6.1)[d]
	648	Lansoprazole 30 mg	65	85	
2	639	KAPIDEX 60 mg	66	85	(2.2, 10.5)[d]
	656	Lansoprazole 30 mg	65	79	

CI = Confidence Interval
[a] Based on crude rate estimates, patients who did not have endoscopically documented healed EE and prematurely discontinued were considered not healed.
[b] Patients with at least one post baseline endoscopy
[c] Primary efficacy endpoint
[d] Demonstrated non-inferiority to lansoprazole

KAPIDEX 90 mg was studied and did not provide additional clinical benefit over KAPIDEX 60 mg.

14.2 Maintenance of Healed Erosive Esophagitis

A multi-center, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed an EE study and showed endoscopically confirmed healed EE. Maintenance of healing and symptom resolution over a six-month period were evaluated with KAPIDEX 30 mg or 60 mg once daily compared to placebo. A total of 445 patients were enrolled and ranged in age from 18 to 85 years (median age 49 years), with 52% female. Race was distributed as follows: 90% Caucasian, 5% Black and 5% other.

Sixty-six percent of patients treated with 30 mg of KAPIDEX remained healed over the six-month time period as confirmed by endoscopy (see Table 6).

Table 6: Maintenance Rates[a] of Healed EE at Month 6

Number of Patients (N)[b]	Treatment Group (daily)	Maintenance Rate (%)
125	KAPIDEX 30 mg	66.4[c]
119	Placebo	14.3

[a] Based on crude rate estimates, patients who did not have endoscopically documented relapse and prematurely discontinued were considered to have relapsed.
[b] Patients with at least one post baseline endoscopy
[c] Statistically significant vs placebo

KAPIDEX 60 mg was studied and did not provide additional clinical benefit over KAPIDEX 30 mg.

KAPIDEX 30 mg demonstrated a higher median percent of 24-hour heartburn-free days compared to placebo over the 6-month treatment period.

14.3 Symptomatic Non-Erosive GERD

A multi-center, double-blind, placebo-controlled, randomized, 4-week study was conducted in patients with a diagnosis of symptomatic non-erosive GERD made primarily by presentation of symptoms. These patients who identified heartburn as their primary symptom, had a history of heartburn for 6 months or longer, had heartburn on at least 4 of 7 days immediately prior to randomization and had no esophageal erosions as confirmed by endoscopy. However, patients with symptoms which were not acid-related may not have been excluded using these inclusion criteria. Patients were randomized to one of the following treatment groups: KAPIDEX 30 mg daily, 60 mg daily, or placebo. A total of 947 patients were enrolled and ranged in age from 18 to 86 years (median age 48 years) with 71% female. Race was distributed as follows: 82% Caucasian, 14% Black and 4% other.

KAPIDEX 30 mg provided statistically significantly greater percent of days with heartburn-free 24-hour periods over placebo as assessed by daily diary over 4 weeks (see Table 7). KAPIDEX 60 mg was studied and provided no additional clinical benefit over KAPIDEX 30 mg.

Table 7: Median Percentages of 24-Hour Heartburn-Free Periods During the 4 Week Treatment Period of the Symptomatic Non-Erosive GERD Study

N	Treatment Group (daily)	Heartburn-Free 24-hour Periods (%)
312	KAPIDEX 30 mg	54.9[a]
310	Placebo	18.5

[a] Statistically significant vs placebo

A higher percentage of patients on KAPIDEX 30 mg had heartburn-free 24-hour periods compared to placebo as early as the first three days of treatment and this was sustained throughout the treatment period (percentage of patients on Day 3: KAPIDEX 38% versus placebo 15%; on Day 28: KAPIDEX 63% versus placebo 40%).

16 HOW SUPPLIED/STORAGE AND HANDLING

KAPIDEX delayed release capsules, 30 mg, are opaque, blue and gray with TAP and "30" imprinted on the capsule and supplied as:

NDC Number	Size
64764-805-11	Unit dose package of 100
64764-805-30	Bottle of 30
64764-805-90	Bottle of 90
64764-805-19	Bottle of 1000

KAPIDEX delayed release capsules, 60 mg, are opaque, blue with TAP and "60" imprinted on the capsule and supplied as:

NDC Number	Size
64764-915-11	Unit dose package of 100
64764-915-30	Bottle of 30
64764-915-90	Bottle of 90
64764-915-19	Bottle of 1000

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

[see FDA-Approved Patient Labeling (17.2)]

17.1 Information for Patients

To ensure the safe and effective use of KAPIDEX, this information and instructions provided in the FDA-approved patient labeling should be discussed with the patient. Inform patients of the following:

KAPIDEX is available as a delayed release capsule.
KAPIDEX may be taken without regard to food.
KAPIDEX should be swallowed whole.

- Alternatively, KAPIDEX capsules can be opened and administered as follows:
  - Open capsule;
  - Sprinkle intact granules on one tablespoon of applesauce;
  - Swallow immediately.

17.2 FDA-Approved Patient Labeling

Patient Labeling for
KAPIDEX (cap-i-decks)
(dexlansoprazole)
delayed release capsules

Please read this information carefully before you start taking KAPIDEX. Also, read this information each time you refill your prescription, in case anything has changed. Remember, this information does not take the place of talking with your doctor.

What is KAPIDEX?
KAPIDEX is a medicine called a proton pump inhibitor (PPI). Take it for as long as your doctor tells you. KAPIDEX reduces the amount of acid in your stomach.

KAPIDEX is used in adults:

- To treat heartburn related to gastroesophageal reflux disease (GERD).
- To heal acid-related damage to the lining of the esophagus (called erosive esophagitis or EE).
- To stop erosive esophagitis from coming back.

What is GERD and EE?
GERD happens when acid from your stomach enters the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste or burping.

In some cases, acid can damage the lining of your esophagus. This damage is called erosive esophagitis or EE.

Who Should Not Take KAPIDEX?
The active ingredient in KAPIDEX is dexlansoprazole. You should not take KAPIDEX if you are allergic to KAPIDEX or any of its ingredients [see What is in KAPIDEX?].

What Should I Tell My Doctor Before and While I Take KAPIDEX?
Tell your doctor about all your medical conditions. Be sure to tell your doctor if you:

- Are pregnant or could be pregnant
- Are breastfeeding
- Have liver problems

Tell your doctor about all your medicines, including any prescription and any non-prescription medicines, herbal remedies, and vitamins.

KAPIDEX and certain other medicines can affect each other. Before taking KAPIDEX, tell your doctor if you are taking:

- ampicillin
- atazanavir
- digoxin
- iron
- ketoconazole
- warfarin

How Should I Take KAPIDEX?
Take this medicine exactly as it was prescribed and for the full length of time.

You can take KAPIDEX with or without food.

KAPIDEX should be swallowed whole.

KAPIDEX capsules can also be opened and the contents sprinkled on a tablespoon of applesauce. Swallow immediately.

If you miss a dose of KAPIDEX, take your KAPIDEX as soon as you remember. If you think you took too much medicine, call your doctor.

What Are the Possible Side Effects of KAPIDEX?
The most common side effects of KAPIDEX were diarrhea, stomach pain, nausea, common cold, vomiting and gas. There are other less common side effects. If you have any symptoms, be sure to tell your doctor about them.

Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using KAPIDEX. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

What Else Should I Know When Taking KAPIDEX?
KAPIDEX may stop your pain and other acid related symptoms, but you could still have serious stomach problems.

General Information
Medicines are sometimes prescribed for conditions other than those listed in the patient labeling. Do not give KAPIDEX to other people, even if they have the same symptoms you have. Ask your doctor about any concerns you may have or if you want more information about KAPIDEX.

Keep KAPIDEX and all other medicines out of the reach of children. Store KAPIDEX at room temperature.

For full product information, call 1-866-985-2743.

What is in KAPIDEX?
Active ingredient: dexlansoprazole.
Inactive ingredients: sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymer, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The capsule shell is made of hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No.2 and aluminum lake; gray contains ferric oxide and aluminum lake; and both contain titanium dioxide.

Distributed by
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

U.S. Patent Nos. - 5,026,560; 5,045,321; 5,093,132; 5,433,959; 6,462,058; 6,664,276; 6,939,971; and 7,285,668.

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All other trademark names are the property of their respective owners.

PI1002 R1; January 2009

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/s/

Donna Griebel
1/30/2009 03:51:19 PM

EXHIBIT D


US006462058B1

(12) **United States Patent**
Fujishima et al.

(10) **Patent No.: US 6,462,058 B1**
(45) **Date of Patent: Oct. 8, 2002**

(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**

(75) Inventors: **Akira Fujishima**, Sanda; **Isao Aoki**, Kawanishi; **Keiji Kamiyama**, Ibaraki, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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§ 371 (c)(1),
(2), (4) Date: **Nov. 3, 2000**

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(52) **U.S. Cl.** **514/338**; 546/273.7
(58) **Field of Search** 546/273.7; 514/338

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(74) *Attorney, Agent, or Firm*—Mark Chao; Elaine M. Ramesh

(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

8 Claims, No Drawings

BENZIMIDAZOLE COMPOUND CRYSTAL

This application is the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

TECHNICAL FIELD

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

BACKGROUND ART

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

DISCLOSURE OF INVENTION

Having chiral sulfurin themolecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl] sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

[1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;

[2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H- benzimidazole;

[3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;

[4] a pharmaceutical composition which comprises the crystal according to the above [1];

[5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;

[6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;

[7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluorbethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidization to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution include per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (−)-mandelic acid, (+)-tartaric acid, (−)-tartaric acid, (+)-1-phenethylamine, (−)-1-phenethylamine, cinchonine, (−)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example,a optically active organic acids such as MTPA [a-methoxy-a-(trifluoromethyl)phenylacetic acid] and (−)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1] heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridinyl] methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzenejjtolue, xylene, etc.), pharmaceutical composition with good repro-

ducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low doses and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burns necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity, and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a. pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants; water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose, α-starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvixnylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate

aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2O$], alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and α-tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin. etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem. and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, of loxacin, ciploxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30° C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

^{1}H-NMR spectra were determined with $CDCl_3$ as the solvent using Varian Gemini-200; data are shown in chemical shift δ (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

Optical rotation $[\alpha]_D$ was determined at 20° C. using the DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6 mm dia.×250 mm, temperature: about 20° C., mobilephase: hexane/2-propanol=80/20 or hexane/2-propanol=85/15, flow rate: 1.0 ml/min, detection wavelength: 285 nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-Kx_α ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following definitions:

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

bs: broad singlet

J: binding constant

EXAMPLES

Reference Example 1

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia.×250 mm, temperature: 30° C., mobile phase: hexane/2-propanol/ethanol=255/35/10, flowrate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20–25 mg). Fractions of optical isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45 pm filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (1.6 g, optical purity>97.6%ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+)-lansoprazole.(1.37 g, optical purity>99.9%ee) as an amorphous substance.

$[\alpha]_D$=+174.3°(c=0.994%, $CHCl_3$)

Reference Example 2

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia. ×500 mm, temperature: room temperature, mobile phase: hexane/2-propanol=85/15, flow rate: 60 ml/min, detection wavelength: 285 mn, single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45 μm filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3%ee) as an amorphous substance.

Reference Example 3

Production of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+)-tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55° C. for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4%ee.

Reference Example 4

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5 kg, 12.7 mol, containing 1.89 g of water), toluene (22 l), water (25 g, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 l, 2.53 mol) was added to this mixture at 50 to 60° C., and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at −5 to 5° C., followed by 1.5 hours of stirring at −5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/triethylamine=50/50/l); adjusted to. pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffrac-

tion interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(3) With stirring, a suspension in acetone (20 l) of 10 the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added. The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.)i mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

Example 1

Crystal of (R)–2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml), which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.–68, F: 15.43, O: 8.66; Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42; ^{1}H-NMR: 2.25 (3H, s), 4.40 (2H, q, J=7.8 Hz), 4.68 (1H, d, J=13.8 Hz), 4.85 (1H, d, J=13.8 Hz), 6.69 (1H, d, J=6.0 Hz), 7.29–7.39 (2H, m), 7.52 (1H, m), 7.81 (1H, m), 8.37 (1H, d, J=6.0 Hz), 11.00 (1H, bs). IR(νcm^{-1}): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163. UVmax($CHCl_3$): 283.7 nm; $[\alpha]_D$=+199.2° (c=0.202%, $CHCl_3$).

TABLE 1

Crystal Data and Structure Refinement Parameters

Molecular formula:	$C_{16}H_{14}N_3O_2F_3S$
Molecular weight:	369.36
Crystal color, habit:	Colorless, tabular
Crystal Dimension:	0.40 × 0.30 × 0.04 (mm)
Crystal system:	Monoclinic
Lattice constants:	a = 8.549(1) (Å) b = 23.350(1) (Å) c = 8.720(2) (Å) β 32 103.90(1) (°) v = 1,689.8(4) (Å)
Space group:	$P2_1$
Z:	4
Density (calculated):	1.452 (g/cm^3)

TABLE 1-continued

Crystal Data and Structure Refinement Parameters	
Effective reflection: number/parameter number:	9.12
R (I ≧ 2σ(I)):	0.036
Flack parameter:	−0.02(2)

Example 2

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml) and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropylether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8%ee).

m.p.: 147.0–148.0° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66; Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22; ^{1}H-NMR: 2.24 (3H, s), 4.38 (2H, q, J=7.8 Hz), 4.74 (1H, d, J=13.6 Hz), 4.87 (1H, d, J=13.6 Hz), 6.68 (1H, d, J=5.8 Hz), 7.26–7.36 (2H, m), 7.45(1H,m), 7.78 (1H, m), 8.35 (1H, d, J=5.8 Hz). IR(vcm^{-1}): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163; UVmax($CHCl_3$): 283.6 nm; $[\alpha]_D$=+180.3° (c=1.004%, $CHCl_3$).

TABLE 2

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37

TABLE 2-continued

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

Example 3

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole) 1.5 Hydrate

Amorphous (R)-2-[[[3-methyl,-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water. (0.15 ml) was added. After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

m.p. : 76.0–80.0° C.; Elemental analysis; Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13; Found: C: 48.52, H: 4.44, N: 10.49.

TABLE 3

X-ray Powder Diffraction Data

2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat.

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M $NaHCO_3$ and orally administered at 30

minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group.
*$p < 0.01$ (versus control group, Steel's test)

Experimental Example 2

The crystals of R (+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions	
Detection wavelength:	UV 275 nm
Column:	YMC Pro C18, 4.6 × 150 mm
Mobile phase:	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethyl amine (63:37:1) to reach pH 7.
Flow rate:	1.0 ml/min
Column temperature:	40° C.
Sample injection volume:	10 μl

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous

Sample	Duration of storage	Description	Content (Residual percentage)
Crystal	1 week	Light-brown	97.0
	2 weeks	Brown	93.8
	4 weeks	Brown	91.7
Amorphous	1 week	Brown	70.8
	2 weeks	Blackish brown	57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax and a greater AUC. than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

2. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

3. A pharmaceutical composition which comprises the crystal according to claim 1 and a pharmaceutically acceptable excipient, carrier or diluent.

4. A pharmaceutical composition which comprises the crystal according to claim 2 and a pharmaceutically acceptable excipient, carrier or diluent.

5. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim 1.

6. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim 1 with a pharmaceutically acceptable excipient, carrier or diluent.

7. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim 2.

8. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim 2 with a pharmaceutically acceptable excipient, carrier or diluent.

* * * * *

EXHIBIT E

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Window Opens:	10/08/2009	**Surcharge Date:**	04/09/2010
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Patent Number: 6462058

Application Number: 09674624

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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,462,058	$900.00	$0.00	03/17/06	09/674,624	10/08/02	11/03/00	04	NO	2635USOP

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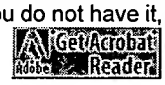

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Exhibit F

Claim and Manner to Read on the Approved Product Kapidex

Claim	Claims of U.S. Patent 6,462,058	Relationship between each claim and the Approved Product
1	A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1 H-benzimidazole wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.	Claim 1 reads on the product[1], i.e., a crystalline form of dexlansoprazole used as an active ingredient of the Approved Product, having a particular crystalline form. A crystalline form of 2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1 H-benzimidazole is included in the final formulation, i.e., the Approved Product by the FDA. The claimed particular crystalline form is the same crystalline form as that used for the NDA of the Approved Product.
3	A pharmaceutical composition which comprises the crystal according to claim 1 and a pharmaceutically acceptable excipient, carrier or diluent.	Claim 3 reads on a pharmaceutical composition, i.e., the Approved Product, including dexlansoprazole in the particular crystalline form.
5	A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim 1.	Claim 5 reads on a method of manufacturing the Approved Product for an intended use.
6	A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim 1 with a pharmaceutically acceptable excipient, carrier or diluent.	Claim 6 reads on a method of using the Approved Product for an intended use.

[1] Use of the terms the "product" is based on the definition under 35 U.S.C 156(f) that the drug product means an active ingredient including any salt or ester of the active ingredient.

Exhibit H

SIGNIFICANT ACTIVITIES UNDERTAKEN BY APPLICANT DURING THE APPLICABLE REGULATORY PERIOD FOR THE APPROVED PRODUCT

Date to FDA	Description
May 28, 2004	Submit phase 1 study (T-P104-069) and nonclinical reports TAK-390MR/00006 and TAK-390MR/00018 as part of Original IND
July 2, 2004	**IND 69,927 effective date for Kapidex (dexlansoprazole MR)**
July 2004 – August 2004	Conduct Phase 1 study (T-P104-069)
July 21, 2004	Submit phase 1 study (T-P104-071)
July 27, 2004	Submit request for Type C Meeting (Development plan)
July 2004 – October 2004	Conduct Phase 1 study (T-P104-071)
October 6, 2004	Telephone conference with the FDA to gain agreements including: transition from Phase 1 to Phase 3, non-clinical study plan , and two phase 1 safety studies to be initiated in December 2004 and January 2005
December 6, 2004	Submit phase 1 study (T-P104-100)
December 28, 2004	Submit phase 1 study (T-P104-092)
December 2004 – January 2005	Conduct phase 1 study (T-P104-100)
January 2005 – February 2005	Conduct phase 1 study (T-P104-092)
March 4, 2005	Submit Type B Meeting Request (End of Phase 2)
April 26, 2005	Submit protocols for 6 phase 3 studies to support three indications (T-GD04-082 and -083, T-EE04-084, -085, -086, and -087) and protocol of long-term safety study (T-GI04-088)
May 12, 2005	End of Phase 2 meeting with the FDA on matters of: discussion of the protocols submitted on April 26, 2005, reviewing data obtained in study T-P104-100, dosage strengths selected for phase 3 studies, statistical analysis plan for secondary endpoints, expectations for additional phase 1 studies, and decision to add 30 mg dosage strength
June 15, 2005	Submit nonclinical amendment (Reports TAK-390MR/00007, TAK-390MR/00008, TAK-390MR/00029, TAK-390MR/00004, TAK-390MR/00017, TAK-390MR/00005, TAK-390MR/00030, TAK-390MR/00175, TAK-390MR/00169, TAK-390MR/00171)

Date to FDA	Description
September 9, 2005	Submit nonclinical amendment (Reports TAK-390MR/00005, TAK-390MR/00002, TAK-390MR/00084, TAK-390MR/00085); and submit amendment 1 of protocols of phase 3 studies (T-GD04-082 and -083, T-EE04-084 and -085, T-EE04-086 and -087, and T-GI04-088)
October 24, 2005	Submit phase 1 study (T-P105-122)
October 24, 2005	Submit CMC information amendment to the IND related to the 30 mg dosage strength
October 27, 2005	Submit CMC information amendment to the IND related to the 30 mg dosage strength
November 11, 2005	Submit phase 1 study (T-P105-115)
November 2005 – January 2006	Conduct phase 1 study (T-P105-122)
December 2005 – November 2006	Conduct phase 1 study (T-P105-115)
December 21, 2005	Submit amendment 2 of protocols for phase 3 studies (T-GD04-082 and -083, T-EE04-084 and -085, T-EE04-086 and -087, and T-GI04-088)
December 22, 2005	Submit request for Type C Meeting (Phase 3 Clinical Program)
December 2005 – May 2006	Conduct two phase 3 studies (T-GD04-082 and -083)
December 2005 – January 2007	Conduct two phase 3 studies (T-EE04-084 and -085)
January 18, 2006	Submit phase 1 study (T-P105-119)
January 2006 – November 2006	Conduct two phase 3 studies (T-EE04-086 and -087)
January 2006 – June 2008	Conduct phase 3 study (T-GI04-088)
February 3, 2006 – February 7, 2006	Conduct phase 1 study (T-P105-119)
March 1, 2006	Telephone conference with the FDA to gain agreements including: design of two additional phase 3 studies including 30 mg dosage strength, implementation plan for phase 3 program, statistical analysis plans, and other clinical study issues
April 6, 2006	Submit amendment 3 of protocols of phase 3 studies (T-GD04-082 and -083, T-EE04-086 and -087, and T-GI04-088) and submit two phase 3 studies (T-EE05-135 and T-GD05-137)
April 19, 2006	Submit request for Type B Meeting (End of Phase 2 CMC)
May 2006 – May 2007	Conduct phase 3 study (T-EE05-135)

Date to FDA	Description
May 2006 – June 2006	Conduct phase 1 study (T-P105-134)
May 4, 2006	Submit clinical amendment of protocol of phase 3 study (T-GD05-137) and submit phase 1 study (T-P105-134)
June 1, 2006	Submit phase 1 study (T-P105-129)
June 8, 2006	Submit phase 1 study (T-P105-139)
June 2006 – July 2006	Conduct two phase 1 studies (T-P105-129 and -139)
June 2006 – December 2006	Conduct phase 3 study (T-GD05-137)
June 20, 2006	End of phase 2 meeting for CMC in a form of fulfilling a written response by the FDA to gain agreements including: manufacturing process and control strategy, stability plan, dissolution method, and no bioequivalence study between the phase 3 formulation and the commercial formulation required
July 7, 2006	Submit phase 1 study (T-P105-133)
July 2006 – September 2006	Conduct phase 1 study (T-P105-133)
July 31, 2006	Submit three phase 1 studies (T-P105-132, T-P105-141, and T-P106-146)
August 2006 – September 2006	Conduct two phase 1 studies (T-P105-132 and T-P105-141)
August 2006 – December 2006	Conduct phase 1 study (T-P106-146)
August 7, 2006	Submit amendment 3 for protocols of phase 3 studies (T-EE04-084 and -085)
October 16, 2006	Submit phase 1 study (T-P106-148)
October 2006 – December 2006	Conduct phase 1 study (T-P106-148)
November 7, 2006	Submit amendment to nonclinical information (Reports Covance 6764-367 and Covance 6764-376)
January 4, 2007	Submit amendment with nonclinical information (Reports 36-278/ge and TAK-390MR/00433)
January 21, 2007	Request for nomenclature review
January 22, 2007	Submit phase 1 study (T-P106-149)
February 2007 – March 2007	Conduct phase 1 study (T-P106-149)
March 2007 – October 2007	Review and prepare the NDA documents by CMC researchers

Date to FDA	Description
March 22, 2007	Submit clinical amendment of protocol for phase 3 study (T-GI04-088)
June 11, 2007	Submit amendment with nonclinical information (Reports Covance 6764-375, Covance 6764-374, 36-297/ge, 36-298/ge, 36-299/ge, 36-319/ge)
June 13, 2007	CMC meeting between TAP (U.S.)/Takeda (Japan) on standard of an active ingredient for Pre-NDA meeting
June 18, 2007	Submit request for Type B, Pre-NDA Clinical/Nonclinical Meeting
June 20, 2007	Submit request for Type B, Pre-NDA CMC Meeting
August 13, 2007	Submit request for Type C Meeting (Pediatric Assessment Plan)
August 21, 2007	Resubmit request for nomenclature review of preferred trade name and alternate trade name.
August 23, 2007	Submit amendment with nonclinical information (Amending Report 36-299/ge)
August 23, 2007	Pre-NDA meeting (CMC)-conference on in vitro and in vivo correlation (IVIVC)
October 1, 2007	Submit amendment with nonclinical information (Report MDS AA30650-01, JCL041081)
October 1, 2007	Pre-NDA meeting (clinical/pre-clinical) – receiving the FDA's request for additional toxicity test
November 2, 2007	Teleconference with FDA to discuss Pediatric Assessment Plan
November 27, 2007	Pre-NDA CMC meeting – follow up meeting
December 10, 2007	Submit amendment with nonclinical information (Reports JCL051462, JCL032491, JCL041042, JCL041051, JCL032241, TAK-390MR/00524, TAK-390MR/00519)
December 28, 2007	**NDA 22-287 submission to the FDA**
December 31, 2007	Date of receipt of submission of NDA by the FDA
January 4, 2008	Received notification from FDA of rejected the preferred trade name
January 15, 2008	Submitting original protocol of phase 1 study (T-P107-164) and phase 3 study (T-GD07-170)
January 2008 – January 2009	Conduct phase 1 study (T-P107-164)
January 2008 – March 2009	Conduct phase 3 study (T-GD07-170)
January 30 – February 1, 2008	Mock Pre-approval Inspection in Osaka
February 5, 2008	Submit amendment with nonclinical information (Reports TAK-390MR/00551, TAK-390MR/00550, TAK-390MR/00549.001A)
February 11, 2008	Receive the FDA's request for the ECG waveforms from clinical study (T-P104-092)

Date to FDA	Description
February 19, 2008	Revise IVIVC (as agreed to in pre-NDA CMC meeting)
March 4, 2008	Uploade ECGs into warehouse
March 13, 2008	Communicate with the FDA to confirm sufficiency of the NDA for review, classification, and the use fee goal date
March 19, 2008	Telephone conference with the FDA (the Cardio-Renal Division) to discuss ECG data. FDA requested re-analysis.
March 26, 2008	Propose to FDA to re-read all ECGs
April 28, 2008	Submit 4-month Safety Update (including updated safety information from T-GI04-088)
April 29, 2008	Submit request for review of trade name Kapidex
May 20, 2008	Receive the FDA's request for information of pooled clinical pharmacology data and adverse events
May 30, 2008	Submit the data to the FDA requested May 20, 2008
June 6, 2008	Receive the FDA's request for additional information of cardiovascular adverse events
June 24, 2008	Submit re-analysis of the ECG data requested on March 19, 2008 to the FDA
June 26, 2008	Submit information of treatment-emergent potential cardiovascular adverse events requested on June 6, 2008 with detailed narratives identified in the 4-month Safety Update to the FDA
June 27, 2008	Receive FDA request for genotyping reports and methods
July 1, 2008	Teleconference with FDA to discuss 27 June 2008 Information Request
July 11, 2008	Submit response to 27 June 2008 Information Request (genotyping)
July 16, 2008	Receive Notice of Inspection from FDA.
August 2008	Conduct pre-approval inspection of manufacturing facilities in Osaka (week of August 11th) and Hikari (August 18-26) in Japan
August 8, 2008	FDA rejected the alternate trade name
August 13, 2008	Receiving the FDA's request for additional cardiovascular information from clinical studies
August 21, 2008	Submit response to the request for additional information received on August 13, 2008
August 26, 2008	Submit response to the request for additional information received on August 13, 2008
August 28, 2008	Receive FDA request for clinical data (bone fracture) and CMC information (CoAs)
September 9, 2008	Respond to clinical information request of August 28, 2008
September 10, 2008	Respond to CMC request of August 28, 2008
September 17, 2008	Receive report from the FDA of tentative approval of Kapidex

Date to FDA	Description
September 26, 2008	Submit revised draft labeling incorporating the Kapidex trade name
October 14, 2008	Receive a request from the FDA for a revised pediatric assessment plan, pediatric waiver request, and deferral request
October 15, 2008	Informed by the FDA to extend the user fee goal date to January 31, 2009
October 15, 2008	Telephone conference with the FDA regarding the proposed IVIVC model and receive a request for revised dissolution specifications.
October 20, 2008	Submit the revised pediatric assessment plan, pediatric waiver request, and deferral request requested on October 14, 2008
October 21, 2008	Submit the revised dissolution specifications requested on October 15, 2008
November 3, 2008	Receive comments from the FDA regarding package insert
November 5, 2008	Receive the FDA's comment regarding packaging component labeling
November 3, 2008 – January 28, 2009	Communicate with the FDA regarding the labeling (package insert and component labeling)
December 17, 2008	The IVIVC methodology was removed from the NDA following the FDA's request
January 30, 2009	**NDA was approved.**